



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No.: 24741-1521

Applicant(s) Bernd GRONER *et al.*

Appl. No.: 09/596,774

Examiner: K. Canella

Filing Date: June 19, 2000

Art Unit: 1642

Title: BIFUNCTIONAL PROTEIN, PREPARATION AND USE

Request for Reconsideration under 37 C.F.R. §1.116

Commissioner for Patents
ATTN: BOX AF
Washington, D.C. 20231

Ok to enter - KAC

Sir:

Applicants herein respond to the Advisory Action mailed January 28, 2003 (Paper No. 18). A Notice of Appeal was filed in this case on January 29, 2003. As this reply is being filed within two months of the filing of the Notice of Appeal (March 29, 2003 was on a Saturday), Applicants believe that no fee is due. Please debit any underpayments, or credit any overpayments, to firm deposit account no. 08-1641.

REMARKS

Claims 2-7, 9-11, 13 and 15 are pending. The advisory action is addressed below.

35 USC §103(a) - Obviousness

The Examiner maintains rejection of claims 2-7, 9-11, 13 and 15 under 35 USC §103(a) as allegedly obvious over Stancovski et al, (Journal of Immunology, 1993, Vol. 11, pp. 6577-6582) in view of Brocker et al (Eur. J. Immunology, 1993, Vol. 23, pp. 1435-1439, reference AA of the IDS filed 9/22/00) and Horgan et al (Journal of Immunology, 1993, Vol. 150, pp. 5400-5407). Applicants note that it appears that the Examiner has inadvertently switched the teachings of Stancovski and Horgan, as it was Horgan who taught the higher affinity to antigen in

constructs with an IgG1 hinge region, and Stancovski who taught a recombinant molecule comprising the variable regions of an anti-erbB2 antibody fused directly to the zeta chain of a T-cell receptor. The Examiner asserts that "it can be concluded from [Horgan] et al that binding affinity is the greatest for constructs having a G1 hinge, > constructs having no hinge, > constructs having a G4 hinge."

Applicants respectfully disagree. Horgan et al teach that intact IgG1 had a greater binding affinity to the peptide CYYYEEEEY than did hinge-deleted IgG1; intact IgG4 bound less well to CYYYEEEEY than did IgG1; and hinge-deleted IgG4 bound to CYYYEEEEY better than intact IgG4 and had an affinity similar to IgG1. Thus, even with respect to this specific peptide (CYYYEEEEY), Horgan does not teach that the inclusion of a G1 hinge results in greater affinity than, for example a hinge-deleted IgG4. Further, there is no teaching that the inclusion of a G1 hinge in all antibodies will result in a higher affinity than, for example, a hinge deleted IgG4, much less that this would be the case in an artificial construct such as a bifunctional protein as described in the present claims.

Nevertheless, the Examiner asserts that "[t]he instant claims do not specify that the hinge region be of a specific type. Therefore one of skill in the art would be motivated to include a hinge region of the G1 type." However, the hinge region of an IgG1 molecule is comprised of only **15 amino acids**. See Meulenbroek, A.J. and Zeijlemaker, W.P., Human IgG Subclasses: Useful diagnostic markers for Immunocompetence (CLB 1996), Section 2.3, Table I <<http://www.xs4all.nl/~ednieuw/IgGsubclasses/subkl23.htm>>. The claims in the present case are directed to constructs with a hinge region comprising from **about 40 to about 200 amino acids**. In other words, even if the Examiner is correct that Horgan teaches that a G1 hinge increases the affinity of all antigen binding molecules and provides a motivation to include a G1 hinge in the construct of Stancovski, the construct that would result would fall outside the scope of the present claims. Accordingly, the combination of Horgan and Stancovski cannot render the present claims obvious, whether there is motivation to combine, or not.

CONCLUSION

In view of the above arguments, Applicants respectfully request the withdrawal of the rejection of the pending claims under 35 U.S.C. §103(a) and that the case be passed to allowance.

Respectfully submitted,

Date: March 31, 2003

HELLER EHRMAN WHITE & MCAULIFFE
1666 K Street, NW, Suite 300
Washington, DC 20006
Telephone: (202) 912-2000
Facsimile: (202) 912-2020

By Brian D. Kaider

Brian D. Kaider
Attorney for Applicant
Registration No. 51,117